Intravenous Vitamin C & Cancer
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Heidi Fritz MA, ND
Research Fellow
Canadian College of Naturopathic Medicine
Historical use

• In 1980, Nobel Prize winner Linus Pauling stated in the New England Journal of Medicine:

  “We are quite confident that, in the not too distant future, supplemental ascorbate will have an established place in all cancer treatment regimes.” (quoted in Block 2003)
First studies of intravenous vitamin C (IVC) in cancer patients conducted in 1970’s by Ewan Cameron & Linus Pauling in Scotland.

- Case series of 50 terminally ill cancer patients receiving high dose IVC reported remarkable survival benefit in some.
  - Cameron 1974.
- Weaknesses: Uncontrolled, case-based
Background

• IVC use among complementary oncology practitioners (Padayatty 2010).
  – Survey of CAM practitioners at annual CAM conferences in 2006 and 2008
  – 84% of CAM practitioners (172 of 199 respondents) reported using IVC for conditions including cancer.
    • Up to 40% of practitioners for breast cancer
    • ~20-30% for other types of cancers
Questions

1. Does IVC improve tumor response, survival time, quality of life of patients with cancer?

3. Is IVC safe in combination with chemotherapy?
Study

Systematic review of all human data (RCT, phase I/II, observational, case based) on the use of IVC and effects on:

1. Response rates
2. Survival
3. Side effects of chemo/ QOL
4. Interactions
Study Flowchart

889 Records selected for initial screen

763 Records excluded after deduplication and title/abstract review

126 Full text articles screened

89 Excluded
33 reviews
53 not cancer related
1 oral vitamin C

37 Articles included for Data Extraction and Analysis

2 RCTs
14 reports of 13 Phase I/11 trials
5 Observational studies
16 Case-based studies
2 RCTs

• Sullivan 2011
  • Kansas University
  • 27 ovarian cancer patients (stage III-IV)
  • IVC + 1st line paclitaxel/ carboplatin
    • VS chemo alone
  • HD-IVC 2x/wk x 6mo during chemo + 6mo post
  • IVC patients had fewer reported SE
    • Controls had 5-fold higher rate of SE
  • Trend toward longer time to relapse

• Dammacco 1992 – multiple myeloma, low dose IVC
Phase I/II Studies

- Stephenson 2013 & 2007
- Mikirova 2012
- Monti 2012
- Welch 2010
- Hoffer 2008
- Mikirova 2007
- Yeom 2007
- Riordan 2005
Phase I/II Studies

• Pharmacokinetic data
• Does IVC achieve therapeutic blood levels?

• 5-40 mM vitC needed for cytotoxic effects (Riordan 1995). Not achievable through oral dosing.

• HD-IVC (50g+) shown to achieve between 18-50 mM.
## Dosing and PK

<table>
<thead>
<tr>
<th>Studies</th>
<th>Dose</th>
<th>Schedule</th>
<th>Blood AA Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stephenson 2013/ 2007</td>
<td>50, 70, 90, and 110 g/m2</td>
<td>4d/wk x4wk</td>
<td>49 mM (max’d at 70 g/m2 dose)</td>
</tr>
<tr>
<td>Mikirova 2012</td>
<td>50g</td>
<td>3x/wk x 6 tx</td>
<td>18 mM</td>
</tr>
<tr>
<td>Monti 2012</td>
<td>50, 70, 100g</td>
<td>3d/wk x 8wk</td>
<td>25.3-31.9 mM</td>
</tr>
<tr>
<td>Hoffer 2008</td>
<td>0.4, 0.6, 0.9 or 1.5 g/kg</td>
<td>3x/wk x 2wk</td>
<td>26 mM</td>
</tr>
<tr>
<td>Riordan 2005</td>
<td>10, 30, 40 or 50g</td>
<td>Daily x 8wk</td>
<td>3.8 mM*</td>
</tr>
</tbody>
</table>

* Administered as a continuous infusion 10-20 mL/h (ie. TKVO vs 250+ mL/h)
## Efficacy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Pop</th>
<th>Chemo/ rad</th>
<th>Tumor response/survival</th>
<th>QOL/ Cancer symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephenso n 2013</td>
<td>Solid tumors</td>
<td>none: EPA 2g</td>
<td>null</td>
<td>maybe</td>
</tr>
<tr>
<td>Mikirova 2012</td>
<td>Several ca types mets</td>
<td>none</td>
<td>CRP ass w PSA</td>
<td>n/a</td>
</tr>
<tr>
<td>Monti 2012</td>
<td>Stage IV pancreatic ca</td>
<td>Gem + erlotinib</td>
<td>T mass 10-40%</td>
<td>n/a</td>
</tr>
<tr>
<td>Sullivan 2011 (RCT)</td>
<td>Stage III-IV ovarian ca</td>
<td>Paclitaxel carboplatin</td>
<td>Trend N=27</td>
<td>Yes 5-fold</td>
</tr>
<tr>
<td>Hoffer 2008</td>
<td>Solid tumors</td>
<td>none</td>
<td>n/a</td>
<td>yes</td>
</tr>
<tr>
<td>Yeom 2007</td>
<td>Stage IV ca</td>
<td>none</td>
<td>n/a</td>
<td>yes</td>
</tr>
</tbody>
</table>
Phase I/II: Anti-tumor & Survival

- Mikirova 2012: tumor markers:
  - In PrCa patients lowered CRP correlated with reductions in the tumor marker PSA.
  - 53% of patients had reductions in CEA, CA 27.29, CA 15.3, but this was not significant.
- Monti 2012: Stage IV pancreatic ca:
  - Tumor mass decreased b/w 10-42% in 8 of 9 patients.
  - Mean progression free survival was 89d; OS 182d.
- Sullivan 2011: stage III-IV ovarian ca
  - Trend to longer time to relapse in IVC group.
Phase I/II: QOL & Symptoms

- Stephenson 2013: QOL seemed to improve for patients who made it to 3-4wk of tx.
- Sullivan 2011: Chemo only pt reported 5-fold higher rate of SE c/t IVC patients.
- Hoffer 2008: Physical function (FACT-G) deteriorated significantly in the lowest dose group ($p<0.001$) but not in the higher dose groups (0.6 g/kg +).
- Yeom 2007: The global health score improved from 36±18 to 55±16 after administration of vitamin C ($p=0.001$). Also improvement in functional scales.
Low dose - MM

- Berenson 2007
- Berenson 2006
- Abou-Jawde 2006
- Wu 2006
- Borad 2005
- Bahlis 2002
- Dammacco 1992 (RCT)

- Safety of low dose IVC (1g) in conjunction with arsenic trioxide, bortezomib, melphalan, dexamethasone.
<table>
<thead>
<tr>
<th>Studies, N=5</th>
<th>Pop</th>
<th>Concurrent chemo/ rad?</th>
<th>Tumor response/survival</th>
<th>QOL/ Cancer symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vollbracht 2011</td>
<td>Early breast ca</td>
<td>Yes*</td>
<td>n/a</td>
<td>yes 2-fold</td>
</tr>
<tr>
<td>Takahashi 2012</td>
<td>Adv cancer</td>
<td>NR</td>
<td>n/a</td>
<td>yes</td>
</tr>
<tr>
<td>Cameron 1991</td>
<td>Adv cancer</td>
<td>no</td>
<td>yes</td>
<td>n/a</td>
</tr>
<tr>
<td>Cameron 1978</td>
<td>Adv cancer</td>
<td>no</td>
<td>yes 5.6-fold</td>
<td>n/a</td>
</tr>
<tr>
<td>Cameron 1976</td>
<td>Adv cancer</td>
<td>no</td>
<td>yes 4-fold</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*See full study description for list of chemo drugs.
Observational data

- Vollbracht 2011
  - Retrospective cohort, n=125 (53 IVC, 72 not)
  - Breast cancer, stage II
  - 7.5g weekly x min 4wk alongside chemo/ rad
  - Significant reduction of chemo SE/ symptoms:
    a) Nausea, loss of appetite
    b) Fatigue
    c) Depression
    d) Sleep disorders
    e) Others

- Symptoms scores ~2-fold higher in control group.
Observational data

• Vollbracht 2011
  • 7.5g weekly x min 4wk along side chemo/ rad
  • Chemo regimes:
    • Epirubicin/ cyclophosphamide (56%)
    • Cyclophosphamide/ methotrexate/ fluorouracil (20%)
    • Fluorouracil/ epirubicin/ cyclophosphamide
    • (15.2%)
Observational data

Takahashi 2012

- Prospective cohort, n=60
- Newly diagnosed with advanced cancer
- Dose not available, x 4wk
- EORTC-QOL global health improved after 2 and 4 weeks (p<0.05).
- Significant improvements in: fatigue, pain, insomnia, constipation, physical, and other function scales.
- Clinical global impression improved up to 60% at 4wk.
Observational data


- 10-30g IVC x ~10d, then oral AA thereafter, indefinitely
- 2 early studies: historical controls
  1. 1976: N=100 cases, 1000 controls
     - Mean survival: 160 days increased for AA group c/t controls (~4-fold increase)
  2. 1978: N=100 cases, 1000 controls
     - Mean survival: 300+ days increased for AA group relative to controls (5.6-fold increase).
  3. 1991: N=294 cases; 1532 controls
     - Mean survival 343 days for AA group c/t180 days for controls (1.9-fold increase)
Case-based data

16 publications reporting on a total of 218 individual cases

1. Cancer remission and long term cancer-free survival
2. Survival well past life expectancy
3. Initial disease stabilization but recurrence/ death after IVC decreased
Case-based data

Fig 2. Number of case reports related to efficacy of HD-IVC
Human Studies: Interactions

- IVC appears to be safe with:
  - Gemcitabine
  - Erlotinib
  - Paclitaxel
  - Carboplatin
  - Arsenic trioxide/ Melphalan
  - Bortezomib
  - Dexamethasone
  - Decitabine
  - Epirubicin/ cyclophosphamide
  - Cyclophosphamide/ methotrexate/ fluorouracil
  - Fluorouracil/ epirubicin/ cyclophosphamide
Mechanism

Preferential tumor cell killing

• At concentrations achievable through intravenous administration, vitamin C generates high levels of the cytotoxic reactive oxygen species (ROS), hydrogen peroxide.

• Tumor cells have up to 10-to-100-fold lower levels of catalase, the enzyme that breaks H2O2, making them much more susceptible to the effects of hydrogen peroxide:

\[ 2 \text{H}_2\text{O}_2 \rightarrow 2 \text{H}_2\text{O} + \text{O}_2 \]
Preferential tumor cell killing

- Vitamin C is preferentially taken up by tumor cells
  - facilitated transport of vitamin C with glucose combined with their increased metabolic need for glucose.
Side Effects

1. Nausea and headache due to osmotic load
   Transient and corrected by eating/ drinking
2. DLTs: 3 incidents of grade 4 hypernatremia, and 2 incidents of grade 3 hypokalemia (Stephenson 2013).
   1. Dr Anderson recommends to administer with chlorides and potassium.
3. Other AE reported not clear if related to underlying disease or concurrent chemotherapy.
Contraindications

1. Glucose-6-phosphate dehydrogenase deficiency due to risk of hemolysis
2. Iron overload (eg. hemochromatosis) d/t increased iron absorption
3. Oxalate stone formers due to risk kidney stone formation
4. There is risk of acute tumour hemorrhage and necrosis in patients with advanced stages of cancer, necessitating gradual dose escalation
5. Patients should supplement with oral vitamin C (<10g/d) between infusions to prevent rebound hypovitaminosis caused by the induction of liver enzymes responsible for ascorbic acid degradation.
Conclusion

• AA anticancer concentrations achievable (Phase I/II)
• IVC may reduce chemo SE cancer symptoms (RCT, observational)
• IVC may improve QOL (Phase I/II, observational)
• IVC may improve disease outcomes alongside paclitaxel/ carboplatin (ovarian cancer) (RCT)
  • survival benefit in advanced cancers (observational, case based)
• Safe in combination with XX chemotherapies (slide 24) (RCT, phase I/II, observational).
• Most common SE appear to be transient nausea or n/a associated with osmotic load. > eating/ fluids.
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